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Intensive Glucose Control in the ICU: Is SUGAR NICE?

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Intensive insulin therapy is extensively used to lower blood glucose concentrations in critically ill patients hospitalized within the intensive care unit. The discovery by the NICE-SUGAR study investigators that tight glucose control in this setting might actually increase mortality has generated considerable discussion about the wisdom of this approach.

Compelling evidence from a 2001 publication[1] showed that intensive insulin therapy to maintain blood glucose concentrations at 4.4–6.1 mmol/l reduced the morbidity and mortality of critically ill patients hospitalized in surgical intensive care units (ICUs). Although a number of subsequent studies were unable to replicate these effects, tight glucose control is now extensively used in hospital ICUs worldwide and is advocated by several clinical organizations. Publication of results from the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial,[2] however, provides further information that is likely to intensify the debate.

The rationale behind the use of insulin therapy in critically ill patients is that severe injury or infection alters carbohydrate metabolism, which results in insulin resistance.[3] Hyperglycemia commonly ensues, even in patients who do not have pre-existing diabetes mellitus. Van den Berghe and colleagues[1] performed a prospective, controlled study of adults who underwent mechanical ventilation in a surgical ICU. Patients were randomly allocated to either intensive insulin therapy (to achieve glucose concentrations of 4.4–6.1 mmol/l) or conventional insulin therapy (to maintain glucose concentrations of 10.0–11.1 mmol/l). Analysis of data from 1,548 patients revealed that maintenance of blood glucose concentrations ≤6.1 mmol/l (the mean morning glucose level was 5.7 mmol/l in the intensive-treatment group) reduced mortality in the ICU by 42% (from 8.0% in the conventional-treatment group to 4.6% in the intensive-treatment group).[1]

These dramatic findings prompted numerous hospitals to institute tight glucose control protocols, which quickly became the 'standard of care'. In many cases, these protocols are also used to manage medical and surgical patients outside the ICU. The latter approach is based, in part, on observational studies that demonstrated poor clinical outcomes in non-ICU inpatients with hyperglycemia. The American College of Endocrinology and the American Diabetes Association, with the participation of prominent cardiology, critical care and anesthesiology organizations, issued a consensus statement that supported intensive glycemic control for inpatients.[4]

Notwithstanding the implementation of these regimens, meta-analyses and systematic reviews have reached opposite conclusions about their efficacy.[5,6] Moreover, some clinical trials fail to observe benefits with tight glucose control. The multinational NICE-SUGAR trial was designed to test the hypothesis that intensive glucose control reduces mortality at 90 days. The study population comprised 6,104 adults admitted to medical or surgical ICUs at one of 42 hospitals in Australia, New Zealand or Canada. Within 24 h of admission, patients who were expected to require 3 or more consecutive days of critical care were randomly assigned to intensive or

conventional glucose control. The target glucose ranges were 4.5–6.0 mmol/l and ≤ 10.0 mmol/l in the intensive and conventional treatment groups, respectively.

The mean time-weighted blood glucose values in the intensive-control group (6.4 ± 1.0 mmol/l) were significantly lower than those in the conventional-control group (8.0 ± 1.3 mmol/l; $P < 0.001$). Unexpectedly, mortality in the intensive-control group was significantly higher than that in the conventional-control group (27.5% versus 24.9%, $P = 0.02$). Severe hypoglycemia (defined as a blood glucose concentration ≤ 2.2 mmol/l) was also higher in the intensive group than in the conventional group (6.8% versus 0.5%). Of note, the excess deaths in the intensive-treatment group were predominantly cardiovascular, which is consistent with evidence from other studies that severe hypoglycemia might be associated with adverse cardiovascular events.[7] In NICE-SUGAR, no appreciable differences were observed between the two groups for other outcomes, such as length of stay in the ICU, total duration of hospitalization, number of days of mechanical ventilation, rate of positive blood cultures or red blood cell transfusion.

When all the available data are considered, an important step is to establish reasons for the discrepancies in the published literature. A meta-analysis of 29 randomized trials (8,432 patients) revealed no difference in mortality between patients assigned to tight glucose control and those assigned to standard glucose control.[5] Individual studies show that tight glucose control protocols in ICU patients result in better, equivalent or worse outcomes than standard glucose control. Factors that might contribute to these disparate results include differences in populations of patients (for example, reasons for admittance to the ICU), insulin-treatment protocols, mortality, glucose goals, glucose concentrations actually achieved, and the use of parenteral nutrition.[5] The expertise and experience of nursing staff at a particular institution could also influence the outcome.

Another critical, but frequently overlooked, factor is the method used to measure glucose levels. In their 2001 study, Van den Berge *et al*.[1] measured glucose in arterial blood with an accurate arterial blood gas analyzer. Many of the subsequent studies used capillary blood and measured glucose with point-of-care meters; however, in numerous publications the sample type and/or method of analysis are not actually specified. Variability in glucose results could be a consequence of differences in the types of specimen analyzed, the method used and/or patient-specific variables (for example, physiology or presence of interfering substances).[8] In NICE-SUGAR, glucose measurements were performed on arterial blood "whenever possible" using "point-of-care or arterial blood gas analyzers or laboratory analyzers in routine use at each center." The different glucose values produced by these diverse methods and samples will lead to different insulin doses and potentially wide variations in the true glucose concentrations among patients. Glucose meters are considerably less precise than blood gas analyzers or central laboratory analyzers. Data from 19,597 sites in College of American Pathologists proficiency tests show large variation.[9] The coefficients of variation among 17 glucose meter types were 12–14%, with bias between two types as high as 41%. Bias of 41% at a glucose concentration of 8.0 mmol/l is equivalent to 3.2 mmol/l, which is twice the difference (1.6 mmol/l) in mean blood glucose concentrations between the intensive and conventional groups observed in NICE-SUGAR. If a glucose meter has high bias (that is, consistently reports higher values than the patient's actual glucose concentration), the patient will receive too much insulin and might develop hypoglycemia (which might not be identified as many of the patients in the ICU are unconscious).

The most widely accepted criteria for adequate glucose-meter performance are that 95% of the time the result should be within ± 20% of the 'true' glucose value at ≥ 4.2 mmol/l and within ± 0.83 mmol/l at glucose concentrations < 4.2 mmol/l.[10] If a patient has a real glucose concentration of 5.3 mmol/l, the acceptable range for a meter would be 4.3–6.4 mmol/l (note that 5% of the time the

results could be outside this range.) These values exceed the range for the intensive control target of 4.5–6.0 mmol/l set by the NICE-SUGAR investigators.

Patient-specific factors also contribute to inaccurate results with glucose meters, especially in individuals who are critically ill. Some glucose meters are affected by partial pressure of oxygen and hematocrit. Reduced tissue perfusion in hypotensive patients results in large differences in glucose concentrations in capillary blood samples, despite minimal alterations in arterial blood samples.[8] Another variable is that the glucose concentrations in arterial, venous and capillary blood all differ. Although these differences are minimal in fasting individuals, postprandial capillary glucose values are 1.1–1.4 mmol/l higher than those in venous blood. Finally, as a consequence of differences in water content, glucose concentrations in plasma are ~11% higher than those in whole blood if the hematocrit is normal. Some, or perhaps all, of these factors might have contributed to the results reported by the NICE-SUGAR investigators.

The NICE-SUGAR trial adds to the accumulating data on the use of tight glucose control protocols in patients in the ICU; however, this study does not 'close the case' on these protocols. Further large trials are necessary if the question of whether intensive insulin therapy improves the outcomes of selected ICU patients is to be unequivocally resolved. As the dose of insulin used in critically ill patients is determined exclusively by their blood glucose value, accurate measurement of glucose concentration is essential to achieve the desired targets and to avoid hypoglycemia. In multicenter trials, a particularly important issue is that glucose measurements among institutions are standardized to avoid variability among patients. Highly accurate measurements of glucose concentration will, therefore, be necessary in future research.